IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of:	Confirmation No.: 5814
Carozzi *et al.*	Group Art Unit: 1638
Application Serial No.: 10/782,141	Examiner: Anne R. Kubelik
Filed: February 19, 2004	Attorney Docket No.: 2916693-017000

For: AXMI-014, A DELTA-ENDOTOXIN GENE AND METHODS FOR ITS USE

Pre-Appeal Brief Request for Review

Dear Members of the Panel:

The enclosed Pre-Appeal Brief Request is filed along with a Notice of Appeal dated July 26, 2010 and is accompanied by payment of a three-month extension of time request and fee.

Pending Claims

Claims 1-11, 19, and 22-23 are pending in this application of which Claims 1, 22, and 23 are independent.

Pending Rejections

Claims 1 and 4-7 stand rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Ben-Dov *et al.* (*Appl. Environ. Microbiol.* 62, pages 3140-3145, 1996) in view of Carlton *et al.* (Mol. Biol. Microb. Differ., Proc. Intl. Spore Conf., 9th, Meeting date 1984, pages 246-252, 1985) and further in view of Applicant's response to the Request for Information under 37 C.F.R. 1.105. Claims 2-3, 8-11, 19, 22-23 stand rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Ben-Dov *et al.* in view of Carlton *et al.* and Koziel *et al.* (U.S. Patent No. 5,625,136). Applicants respectfully disagree and request withdrawal of the rejections.

(1) Rejection of Claims 1 and 4-7 under 35 U.S.C. § 103(a) over Ben-Dov *et al.* in view of Carlton *et al.* and in view of Applicant's response to the Request for Information under 37 C.F.R. 1.105

(a) One of ordinary skill in the art would have no motivation to combine Ben-Dov *et al.* together with Carlton *et al.*

At the outset, the Examiner impermissibly uses Applicant's Specification as a basis for the rejection. Specifically, the Examiner requested source information under 37 C.F.R. 1.105 and

subsequently used this information as a basis for the obviousness rejection under 35 U.S.C. § 103(a).[1] However, outside of Applicant's Specification, one of ordinary skill in the art would have no reason to select and isolate sequences from HD536 given the numerous possibilities of well-known strains exhibiting insecticidal activity. Moreover, the only motivation for even considering sequences isolated from HD536 comes from the instant disclosure and not the cited references. Without a specific teaching or motivation, one of ordinary skill in the art would not even look to Carlton *et al.* to choose a strain, let alone select HD536 from the laundry list of possibilities included in Carlton *et al.*

Ben-Dov *et al.* does not teach or suggest all of the claimed elements. The Examiner acknowledges that Ben-Dov *et al.* alone is deficient to render the claims obvious and states that "Ben-Dov et al. do not teach a nucleic acid encoding SEQ ID NO: 1, 2 or 4." Final Office Action at page 4. At best, Ben-Dov *et al.* teach cloning of large restriction fragments from *Bacillus thuringiensis* subsp. *israelensis* and identification of known toxins using Southern hybridization and probes specific for the known toxins. Ben-Dov *et al.* does not teach or suggest a nucleic acid molecule encoding polypeptide with activity against lygus pests, let alone the claimed sequences. Rather, Ben-Dov *et al.* is concerned with characterizing a single 125-kilobase plasmid containing genes that encode delta-endotoxins with activity against mosquito larvae. Ben-Dov *et al.* at page 3140.

Carlton *et al.* evaluates a large number of *Bacillus thuringiensis* strains for the presence of extrachromosomal DNA by agarose gel electrophoresis. Carlton *et al.* at page 251 and Figure 1. In doing so, Carlton *et al.* sets forth a laundry list of *Bacillus thuringiensis* plasmids, including HD536, together with the estimated size of the plasmids in Table 1. Carlton *et al.* at Table 1. In rejecting the claims, the Examiner cites to Table 1 and states that "Carlton et al. teach that strain HD536 has a 68 MDa plasmid implicated in toxin production." *Id.* The Examiner further asserts that "it would have been obvious to one of ordinary skill in the art to modify the method of cloning delta-endotoxin genes from *B. thuringiensis* plasmids as taught by Ben-Dov et al, to clone delta-endotoxin genes from strain HD536 described in Carlton et al." *Id.* The Examiner also states that "[o]ne of ordinary skill in the art would have been motivated to do so because an increased

---

[1] Applicants respectfully note that the response to the Request for Information under 37 CFR 1.105 was submitted to the USPTO and was labeled as proprietary material with the label "DO NOT SCAN." Applicants respectfully disagree with the Examiner's inclusion of this material in the Final Office Action dated January 26, 2010.

repertoire of delta-endotoxins would be desirable for increasing toxicity spectra and for overcoming pest resistance to existing endotoxins." *Id.* Applicants respectfully disagree.

One of ordinary skill in the art would have no motivation to combine the teachings of Ben Dov *et al.* with Carlton *et al.* in a manner that renders the claims obvious. For one, Ben Dov *et al.* is limited to evaluating a specific 125-kilobase plasmid containing known genes that encode delta-endotoxins with activity against mosquito larvae. Ben-Dov *et al.* at page 3140. To achieve this, Ben-Dov *et al.* utilizes probes capable of specifically identifying genes of interest that encode delta-endotoxins with specific activity against mosquito larvae. Ben-Dov *et al.* provides no additional motivation to apply this methodology to toxins other than those that are active against mosquito larvae. Ben-Dov *et al.* also acknowledges that "[a]mbiguous results were obtained with several additional probes (data not shown)…", thus indicating further uncertainty regarding the methodology and applicability of the teachings of Ben-Dov *et al.* Given the above, one or ordinary skill in the art would have no motivation to modify and apply the methodology of Ben-Dov *et al.* to other plasmids, such as those set forth in Carlton *et al.*, with a reasonable expectation of success.

An "obvious to try" rationale may only support a conclusion that a claim would have been obvious where one skilled in the art is choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success. *KSR Int'l Co. v. Tele-flex Inc.*, 550 U.S. 389 (2007). One of ordinary skill in the art would recognize that there was no reasonable expectation of success in obtaining any toxin genes from HD536 since no insecticidal activity was demonstrated for this strain prior to the Applicant's disclosure. Outside of providing a loose correlation between the ~68 MDa plasmid of HD536 and "toxin production," Carlton *et al.* fails to suggest that genes isolated from HD536 would have any insecticidal activity. Instead, Carlton *et al.* merely suggest that the 68 MDa plasmid present in strain HD536 may be responsible for crystal protein production. The presence of a crystal protein provides no evidence for the presence of a gene or encoded protein having insecticidal activity against any pest, particularly any lepidopteran pest.

(b) One of ordinary skill in the art would have no motivation to use the specific probes of Ben-Dov *et al.* to isolate SEQ ID NO:1-5 from HD536

In rejecting the claims, the Examiner cites to Carlton *et al.* and states that "knowledge that the 68 KDa plasmid encodes a toxins would motivate one of skill in the art to sequence the plasmid to search for the toxins genes." Final Office Action at page 5. Applicants respectfully disagree.

One of ordinary skill in the art would have no motivation to use the methodology and specific probes of Ben-Dov *et al.* in an attempt to isolate any one of claimed SEQ ID NO:1-5 from HD536. For one, the claimed sequences have a low sequence homology with other known toxins (<30%). As such, one of skill would not have used the cryIVA, cryIVB, cryIVC, cryIVD, and cytA, probes taught in Ben-Dov *et al.* to isolate any sequence from HD536, let alone the claimed sequences. In fact, only the cryIVA probe was able to detect any gene other than itself, and Ben-Dov *et al.* appears to attribute this cross-reactivity with the degree of sequence homology between the two genes. *See* Ben-Dov *et al.* at column 2, page 3143. Outside of pure conjecture, it is not clear how one of skill in the art would be able to use the hybridization method disclosed by Ben-Dov *et al.* to isolate the sequences of the invention.

(c) <u>One of ordinary skill in the art would have no motivation to try and isolate the claimed sequences from HD536 of Carlton *et al.*</u>

A person of ordinary skill in the art would have no motivation to specifically select and isolate sequences from HD536, especially given the laundry list of plasmids described in Carlton *et al.* Additionally, HD536 is only mentioned once in Table 1 and Carlton *et al.* does not specifically indicate why it would be advantageous to isolate sequences from HD536, let alone the claimed sequences. As there is no structural similarity between the known cry toxins identified by Ben-Dov *et al.* and the claimed sequences, a person of ordinary skill in the art would not looked to the methodology of Ben-Dov *et al.* in an attempt to isolate the sequences of the instant invention from HD536.

(d) <u>AXMI-014 unexpectedly exhibits insecticidal activity against *Trichoplusia ni*</u>

For at least the reasons set forth above, Applicants submit that the Examiner has failed to provide a *prima facie* case of obviousness. However, irrespective of this, secondary considerations of the advantageous properties of the claimed sequences, particularly the broad insecticidal activities of the recited sequences, provide additional support for the nonobviousness of the pending claims. For instance, Example 8 of the Specification provides evidence of the insecticidal efficacy of AXMI-014 against *Trichoplusia ni*. Specification, for example, at page 37, line 18 – page 38, line 3. As set forth in Example 8, samples containing the AXMI-014 protein in *Bacillus* yield a mortality rate of 100% against *Trichoplusia ni* relative to a 0% mortality rate for the control. Specification at Table 2. This result is particularly unexpected given the relatively low amino acid

identity of AXMI-014 as compared to the 18 exemplary endotoxin classes described in Table 1 of the Specification (<30%). Specification, for example, at page 36, lines 1 – 20.

(2) Rejection of Claims 2-3, 8-11, 19, 22-23 under 35 U.S.C. § 103(a) over Ben-Dov *et al.* in view of Carlton *et al.* and Koziel *et al.*

In rejecting Claims 2-3, 8-11, 19, 22-23 under 35 U.S.C. § 103(a), the Examiner acknowledges that "Ben-Dov et al in view of Carlton et al do not teach plants and seeds transformed with the nucleic acid." Final Office Action at page 6. However, the Examiner cites to Koziel *et al.* and asserts that "[a]t the time the invention was made, it would have been obvious to one of ordinary skill in the art to transform the nucleic acid taught by Ben-Dov et al in view of Carlton et al into plants, including maize, as described in Koziel et al." *Id.*

For at least the reasons set forth above, Applicants respectfully disagree with the Examiner's rejection of Claims 3, 8-11, 19, 22-23. Moreover, one of ordinary skill in the art would have no motivation to transform the nucleic acids taught by Ben-Dov *et al.* in view of Carlton *et al.* into plants or cells, let alone the specific claimed plants and cells. For one, Ben-Dov *et al.* has no association with plants and is solely concerned with isolating genes that encode toxins that are active against mosquito larvae. Ben-Dov *et al.* at page 3140. Accordingly, the emphasis in Ben-Dov *et al.* is centered around human infectious diseases as compared to plants or plant cells. *Id.* Outside of including HD536 in a list and describing a loose correlation between HD536 and toxin activity, Carlton *et al.* provides no motivation for including SEQ ID NO: 1, 2, 3, 4, or 5 in plants or cells. Koziel *et al.* fails to remedy the deficiencies of both Ben-Dov *et al.* and Carlton *et al.* and does not suggest transforming the claimed sequences into plants or cells.

For at least the above, withdrawal of the rejections is respectfully requested.

July 26, 2010
Customer No.: **95725**

Telephone: 202-508-3400

Respectfully submitted,

/DAVID L. VANIK/
David L. Vanik, Ph.D.
Registration No.: 64,547

Susan E. Shaw McBee
Registration No. 39,294